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| EXAMINER | |
|---|---|
| JAISLE, CECILIA M | |

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| 1624 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/590,786 | GIELEN-HAERTWIG ET AL. | |
| | Examiner | Art Unit | |
| | Cecilia M. Jaisle | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-14 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 21-23* is/are rejected.

7)☒ Claim(s) *6-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-02-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED OFFICE ACTION**

***Rejections Under 35 USC 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement to treat acute and chronic inflammatory, ischemic or remodeling processes in a human or animal (claim 21), chronic obstructive pulmonary disease (COPD), acute coronary syndrome, acute myocardial infarction or heart failure development (claim 22) or inhibit neutrophil elastase in a human or animal (claim 23). The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The following reasons apply to this enablement rejection.

Many diseases said to be controlled by the claimed compounds, such as COPD, are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases. See Eur. Resp. Soc., <http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx>, downloaded 1/15/08, "... there are currently no effective treatments for COPD ..."

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909

(BPAI 1981). See *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) about types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is not sufficient to enable the claimed methods based solely on the disclosed activity.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration to determine if sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) claim breadth; (2) nature of the invention; (3) state of the prior art; (4) level of predictability in the art; (5) amount of direction provided by the inventor; (6) presence of working examples; and (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing PTO's determination that claims to methods for hepatitis B surface antigen detection did not satisfy enablement requirement). *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that this disclosure fails to satisfy the enablement requirement.

1. **Breadth of the claims:**

**(a) Scope of the methods.** The claims cover pharmaceutical methods using thousands compounds of Formulas (I) and (IA) in which A is phenyl.

**(b) Scope of the diseases covered.** The diseases construed by the claims have been described above. The specification fails to identify results of treatment with the methods of this invention in humans and non-murine animals.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is considered an unpredictable factor. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

*Plant Genetic Systems v. DeKalb Genetics*, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

Regarding NE inhibition and COPD, Roghanian, et al., Am. J. Respir. & Crit. Care Med., Vol. 174, 2006, 1189-1109, describe an area for future clinical research:

> In conclusion, our data show that NE and NE-containing secretions from patients with COPD [chronic obstructive pulmonary disease] or CF [cystic fibrosis] can disable DC [dendritic cell] function by interfering both with the ability of immature DCs to mature in response to bacterial LPS stimulation, and by reducing the antigen-presenting activity of mDCs. Although the in vivo effects of these changes remain to be investigated, the reduced Th1 cytokine levels includes by NE treatment of CDs may, in part, explain the reported Th2 imbalance in the lung immune response to bacteria in patients with CF and the reported loss of IFN-λ-secreting cells in patients with COPD. This local Th2-biased phenotype may be instrumental in the inability of these patients to clear semifacultative intracellular pathogens in the lung … as suggested recently by a variety of animal and human studies. In that context, our strategy of overexpression of the elastase inhibitor, elafin, could be dually advantageous by inhibiting NE and, as shows recently, by providing a Th1-biasing signal in the lungs.

Regarding NE inhibition and acute coronary syndrome, Hsieh, et al., Bioorg. & Med. Chem. Lett., 17 (2007) 1812-1817, state, "Arterial thromboembotic diseases, for example, acute coronary syndrome and ischemic stroke, which are caused by platelet aggregation, are the major causes of death in developed countries." Hsieh tested the 2-benzoylamino-benzoid acid derivates, 6d and 6e (Table 2), and reported, "[C]ompounds 6d and 6e exhibited dual inhibitory effects on platelet aggregation and NE release; therefore, these two compounds may represent new leads for development as anti-inflammatory and anti-platelet aggregatory agents."

Regarding NE inhibition and acute myocardial infarction, Vermeylen, et al., J. of Thromb. & Haemosta., 3: 1955-1961, 2005, reported, "Specific neutrophil elastase inhibition in the lung did not affect lung inflammation, but reduced peripheral

thrombogenicity, suggesting that in this instance neutrophil elastase could have a role as platelet 'primer', as suggested by previous *in vitro* investigations."

Regarding NE inhibition and heart failure, Kyne, et al., Am. Heart J., 139(1):94-100, 2000, reported:

> The results suggest that relative neutrophilia may serve as a simple, noninvasive marker to identify patients who are at high risk for development of CHF [congestive heart failure] after myocardial infarction. If the peripheral neutrophil count truly reflects the myocardial inflammatory response, future interventions that are designed to limit this response could help to reduce morbidity and mortality rates associated with CHF occurring after AMI [acute myocardial infarction].

The ability of an agent that exhibits activities shown in the specification to treat all diseases-conditions construed by the claim, especially in humans and non-murine animals, remains open to further study and proof.

5. **Working Examples:** Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** Roghanian, Hsieh, Vermeylen, Kyne and Europ. Respir. Soc. question the ability of a single class of compounds to effectively treat all types of diseases and/or conditions construed by the claims; they confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained

above. The state of the art, as discussed herein, indicates the requirement for undue experimentation.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

***Response to Remarks of 03-02-2009***

According to *U.S. v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." The above discussion amply describes this test has not been met on this record. In accord with MPEP 2164.04, the above discussion supports this position that there are many reasons to doubt the object truth of the statements contained in this application; they cannot be relied on for enabling support.

Applicants refer to the teachings in the specification and these have already been studied and discussed herein in great detail and have been further studied and discussed in light of the teachings of the prior art cited above.

Applicants are correct in citing *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970) for the proposition that the specification need not contain a working example. However, if the enabling disclosure of a specification is not commensurate in scope with the subject matter encompassed by the claims, as is the case with the present claims, the claims are based on an insufficient disclosure (35 U.S.C. 112, first paragraph) and should be rejected on that ground.

Roghanian, Hsieh, Vermeylen, Kyne and Europ. Respir. Soc., all discussed in detail above, well call into question the ability of the present class of compounds to effectively treat all types of diseases and/or conditions construed by the claims; they confirm the need for additional research. Applicants make no comment thereon.

*Sitrick v. Dreamworks LLC*, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all embodiments. "Because the asserted claims are broad enough to cover both embodiments, the specification must enable both embodiments." The claims at issue cover many embodiments and do not enable all of them.

*Automotive Tech. Int'l. v. BMW of N. America, Inc.*, 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one embodiment. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both embodiments, which the specification fails to do." Here, the claims at issue cover many embodiments and do not enable all of them.

***Obvious Double Patenting Rejection***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 225 USPQ 645

(Fed. Cir. 1985); *In re Van Ornum*, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 and 21-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over pending claims 1-21 of US 10/527391. Although the present claims are not identical to claims 1-21 of US 10/527391, they are not patentable distinct from each other because the present claims substantially overlap the compounds of claims 1-21 of US 10/527391. The compounds of the formula (I) of claims 1-21 of US 10/527391 have the same formula (I) as the compounds of the present claims and the definitions of each of the variables overlap or are co-extensive with each other. It would have been obvious to one of ordinary skill in the art at the time of the invention to select any compound from claims 1-21 of US 10/527391 and use those compounds, because the skilled artisan would have had the reasonable expectation that the species of the genus of claims 1-21 of US 10/527391 would have similar properties and thus the same use as the compounds of the present claims, i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the presently claimed compounds from the genus in claims 1-21 of US 10/527391 because such compounds would have been suggested by the reference as a whole. The claims are prima facie obvious over one another and a

reference rendering the claims of one application obvious would also render the claims of the other obvious and this would be obvious to one of ordinary skill in this art.

Applicants again request that this requirement be held in abeyance until claimed subject matter is deemed allowable.

***Objected Claims – Allowable Subject Matter***

Claims 6-14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Following is an examiner's statement of reasons for indication allowable subject matter.

Claims 6-14 are not anticipated or rendered obvious by Namazi, which describes 5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-methyl-3-[(4-methylphenyl)sulfonyl]-4-(3-nitrophenyl)-2-oxo-1-phenyl-, ethyl ester, having no disclosed utility. In addition, Claims 6-14 are not anticipated or rendered obvious by any of the other prior art of record, whether taken individually or in any combination.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
Cecilia M. Jaisle

**/James O. Wilson/**
**Supervisory Patent Examiner, Art Unit 1624**